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RESEARCH ARTICLE

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Abstract Anatomical and electrophysiological studies have demonstrated up–down asymmetries in vertical ocular motor pathways. We investigated whether these asymmetries extend to the capacity for short-term adaptation of the vertical vestibulo-ocular reflex (VVOR) in humans. Specifically, we asked whether smooth pursuit signals are sufficient to asymmetrically adapt the VVOR. Healthy human subjects ($N = 8$), positioned 90° left-ear-down and fixating with their eyes upon a small laser dot (diameter: 0.1°) projected on a sphere (distance: 1.4 m) were trained toward low VVOR gain for 30 min with symmetric and asymmetric visual VVOR cancellation paradigms, while being oscillated (0.2 Hz, ±20°) on a motorized turntable about the interaural earth-vertical axis. During asymmetric VVOR cancellation, the target was head-fixed in either the pitch-up or pitch-down half-cycles of oscillation (= trained direction) and space-fixed during the other half-cycles (= untrained direction). During symmetric VVOR cancellation, the target was head-fixed throughout the oscillations. Before and after adaptation, the pitch-up and pitch-down VOR gains were assessed during turntable oscillation in complete darkness. Before adaptation, average gains of pitch-up (0.75 ± 0.15 SD) and pitch-down (0.79 ± 0.19 SD) VOR were not significantly different (paired t test: $P > 0.05$). On an average, relative gain reductions induced by selective pitch-up (pitch-up VOR: 32%; pitch-down VOR: 21%) and pitch-down (pitch-up VOR: 18%; pitch-down VOR: 30%) VOR cancellation were significantly ($P < 0.05$) larger in the trained than in the untrained direction. Symmetric visual VVOR cancellation led to a significantly ($P < 0.01$) larger relative gain reduction of the pitch-down (41%) than the pitch-up (33%) VOR. None of the paradigms led to significant changes of phase or offset. We conclude that, in human subjects, the smooth pursuit system is capable to asymmetrically decrease the gain of the VVOR equally well in both the upward and downward direction. The unexpected asymmetric decrease of the VVOR gain after symmetric visual cancellation may be related to the directional preferences of vertical gaze–velocity sensitive Purkinje cells in the flocculus for the downward direction.

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Introduction

While the ocular motor system is right–left symmetric, anatomical and electrophysiological studies documented vertical asymmetries in various species (Ito et al. 1977; Darlot et al. 1981; Matsuo and Cohen 1984; Snyder and King 1988). In healthy humans, eye movements evoked by vestibular or optokinetic stimuli show intraindividual differences between up and down, but no significant directional asymmetries appear when data are pooled over larger human populations (Baloh et al. 1986; Demer 1992). However, consistent vertical asymmetries of the human ocular motor system become evident in disease. For instance, in patients with internuclear ophthalmoplegia, the vestibulo-ocular reflex (VOR) elicited by head impulses in the direction of the anterior semicircular canals (SCC) is relatively well preserved, but impaired in the direction of the

posterior canals (Cremer et al. 1999). Furthermore, patients with atrophy of the vestibulo-cerebellum typically exhibit downbeat nystagmus (DBN) and show better preservation of upward smooth pursuit eye movements (Zee et al. 1974, 1976; Halmagyi et al. 1983). These and other findings in patients with brainstem or cerebellar diseases suggest the existence of inherent asymmetries in human vertical ocular motor pathways, which, in the absence of disease, may be counterbalanced by intact function of specific neural structures.

In healthy humans, asymmetries of vertical ocular motor pathways may be unmasked by direction-specific adaptation of eye movements, for example, of the VOR. Ongoing recalibration, i.e. adaptation, of the VOR gain is indispensable to compensate for changes in the ocular motor system, which occur due to development, aging or disease. Under experimental conditions, VOR gain adaptation can be induced by exposure to visual–vestibular mismatch paradigms (Melvill et al. 1988; Demer et al. 1989; Paige and Sargent 1991). A mismatch between vestibular and visual stimulation leads to slippage of the target image on the retina and indicates inappropriate VOR behavior. The mismatch signal, in turn, is used to recalibrate the VOR gain.

In recent years, numerous studies on VOR motor learning have focused on the vertical VOR (VVOR) because of its behavioral simplicity (e.g. little effect of vergence) and well-defined anatomical connections (Baloh and Demer 1991; Peng et al. 1994; Viirre and Demer 1996). Asymmetric VVOR adaptation has been attempted in squirrel monkeys; by using an optokinetic visual stimulus moving with the turntable in one direction (visual VOR cancellation) and opposite to the turntable in the other direction, upward and downward VVOR gains were modified in a reciprocal fashion, i.e. VVOR gains increased in one direction and decreased in the other direction (Hirata et al. 2002). This finding indicated that, in monkeys, control mechanisms for upward and downward VVOR gain allow direction-specific modifications.

However, asymmetric VVOR adaptation has not been tested in humans so far, and it remains unclear, whether the capacity for direction-specific VVOR adaptation is different for upward and downward directions. In the present study, we investigated the human capacity for asymmetrical short-term VVOR adaptation using a smooth pursuit stimulus and asked specifically, whether selective upward or downward VVOR cancellation would be equally effective, and whether symmetric VVOR cancellation would lead to gain reductions of similar magnitudes in both directions. Since the optokinetic nystagmus in humans is dominated by the smooth pursuit system (Leigh and Zee 1999), human subjects should be able to asymmetrically adapt VVOR gains by fixing their gaze upon a dot that moves with the head in one direction, but stays space-fixed in the other direction.

Methods

Definition

Previous studies on VOR adaptation in humans used the expression ‘short-term adaptation’ to describe changes of gain and phase induced by visuo-vestibular mismatch paradigms lasting around 20 min (Kramer et al. 1998; Shelhamer et al. 1994; Tiliket et al. 1994; Trillenberg et al. 2003). In the present paper, we use the same expression in its descriptive sense, i.e. without implying an underlying mechanism for the VOR changes.

Subjects

Eight healthy subjects (six female; 24–36 years old) gave their informed consent to participate in this study. The experimental protocol was approved by a local ethics committee at Zurich University Hospital, and adhered to the Declaration of Helsinki for research involving human subjects. All subjects were free from disease and none of them were taking any medication at the time of the experiments.

Experimental setup

Subjects were seated upright on a three-axes motor-driven turntable (Acutronic, Jona, Switzerland) with the head restrained by an individually molded thermoplastic mask (Sinmed BV, Reeuwijk, The Netherlands). After the chair was rotated to the 90° left ear down position (LED), subjects were oscillated about the interaural, earth-vertical axis. This stimulus isolates the vestibular response to the semi-circular canals, i.e. the otolith input remains constant. By way of two computer-controlled mirror-galvanometers, a laser dot (diameter: 0.1°) was projected onto a sphere with a radius of 1.4 m from the center of the head.

Eye movement recordings

Eye movements were recorded monocularly using dual search coils (Skalar Instruments, Delft, The Netherlands). The coil frame around the head (side length: 0.5 m) generated three orthogonal digitally synchronized magnetic wave field signals of 80, 96 and 120 kHz. A digital signal processor computed a fast Fourier transform in real time on the digitized search coil signal to determine the voltage induced on the coil by each magnetic field (system by Primelec, Regensdorf, Switzerland). Coil orientation could be determined with an error of less than 7% over a range of ±30°, and with a noise level of less than 0.05° (root mean squared deviation). Eye position signals were digitized at 1,000 Hz per channel with 12-bit resolution.

Search coil annuli were calibrated (Bergamin et al. 2001) and then placed around the cornea of the right or left eye after local anesthesia with oxybuprocaine 0.4%. Adaptation paradigms were performed without eye movement recording. Some subjects remained in the left-ear down position for reinsertion of the search coil annulus after adaptation in order to minimize additional vestibular stimulation; those in whom the annulus was difficult to reinsert were slowly brought back to upright position for the proper placement of the annulus, and then immediately returned to the ear-down position.

Experimental paradigms

We measured the gain of the VVOR before and after adaptation to visual–vestibular mismatches. During both the VVOR testing and adaptation paradigms, subjects were sinusoidally oscillated about the interaural earth-vertical axis (frequency: 0.2 Hz; amplitude: ±20°; peak velocity: 25.1 deg/s, duration: 24 cycles). VVOR testing was performed in complete darkness, while subjects were instructed to try keeping their gaze straight ahead with respect to an imagined spaced-fixed target. Adaptation paradigms lasted 30–40 min, depending on the strain experienced by the subjects.

Figure 1 depicts the three different adaptation paradigms that were used to decrease the gain of the VVOR: (1) symmetric visual VVOR cancellation (left column); (2) selective visual cancellation of the upward VOR (middle column); (3) selective visual cancellation of the downward VOR (right column).

Chair and head oscillation (upper row, 'head') were identical during all three paradigms. During symmetric visual VVOR cancellation (left column), the laser ('target') was head-fixed throughout the oscillation, i.e. the eye-in-head movements (lower row, 'eye') were minimal. During asymmetric VVOR cancellation, the laser was head-fixed only during the head movement in one direction (=trained direction), but remained earth-fixed during the head movement in the other direction (=untrained direction). Thus, during selective visual cancellation of pitch-up VOR (middle column), eye-in-head movements were minimal during upward head movements (trained direction), whereas eye-in-head movements were compensatory during downward head movements (untrained direction). For selective visual cancellation of the downward VOR (right column), eye-in-head movements were minimal during pitch-down head movements (trained direction), whereas eye-in-head movements were compensatory during pitch-up head movements (untrained direction).

Data analysis

Calibrated eye position from the right eye was processed with interactive programs (written in MatLab; The Math Works, Natick, MA, USA). We represent eye positions as 3D rotation vectors in a head-fixed coordinate system. Rotation vectors were smoothed, and angular eye velocity was computed as described previously (Hepp 1990). To obtain representative vertical eye-movement responses, we overlaid the vertical

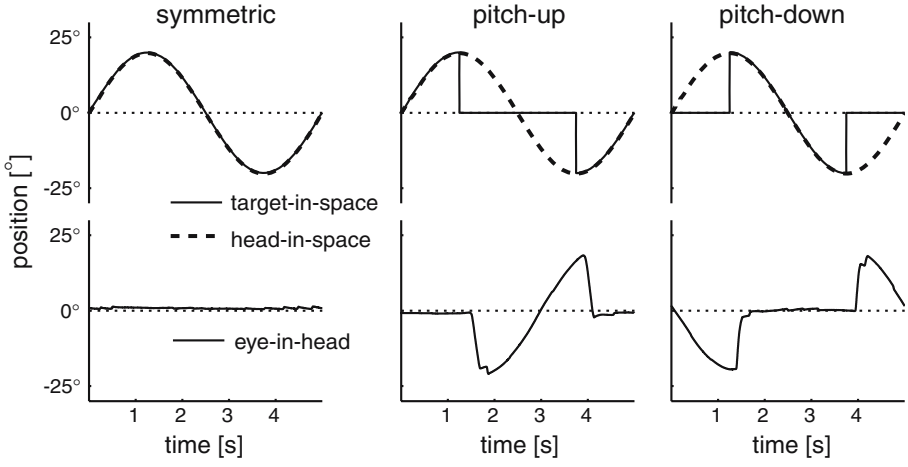

Fig. 1 Training tasks to induce short-term adaptation of the vertical vestibulo-ocular reflex (*VVOR*) by symmetric (*left column*) and asymmetric (*middle and right column*) visual VVOR cancellation. For each of the three VVOR adaptation paradigms, corresponding head ('head-in-space', *upper row*, *dashed line*) and vertical eye positions ('eye-in-head', *lower row*) of a typical subject (*S.M.*) are shown for one oscillation cycle (0.2 Hz, ±20°) about the earth-vertical interaural axis. *Positive values* for position (abscissa) indicate upward head (with reference to head upright position) and eye (with reference to primary position gaze) positions. A small laser dot ('target-in-space', *upper row*, *solid line*) was moved with the head (head-fixed stimulus) or remained earth-fixed (space-fixed stimulus). For symmetric VVOR cancellation (*left column*), the laser was head-fixed throughout the oscillation cycle. For selective cancellation of the pitch-up VOR (*middle column*), the laser was head-fixed during the pitch-up VOR and earth-fixed during the pitch-down VOR. For selective cancellation of the pitch-down VOR (*right column*), the laser was head-fixed during the pitch-down VOR and earth-fixed during the pitch-up VOR

angular-velocity vectors of the cycles and computed the median value for each millisecond (Schmid-Priscoveanu et al. 2000). Recall that subjects were oscillated for 2 min, so the median trace was typically computed from at least 12 cycles. In this way, eye-velocity signals during quick phases were implicitly discarded.

Because we were expecting asymmetric gain changes of VVOR, we anticipated that after adaptation the eye velocity response to a sinusoidal modulation of head position would not itself be sinusoidal. In the extreme case, gain in one direction would be normal, and in the other direction zero, although we expected some intermediate result. A straightforward measure of VVOR gain, such as fitting sine curves to the data, would not give satisfactory results. We also needed to account for any eye velocity bias that our adaptation procedure might induce. For example, even in healthy subjects, the eyes tend to drift vertically in the dark (Bisdorff et al. 2000; Marti et al. 2002), and since this bias drift could have a vestibular origin, we anticipated that our adaptation procedure could change the bias. Figure 2 illustrates the computation of the directional VOR gain for a hypothetical case with a velocity bias of −5 deg/s. The velocity bias was defined as the median eye velocity of the entire oscillation cycle and separates the data into upward and downward directions. After subtracting the median eye velocity, the cumulative change in upward and downward eye position was computed by integrating the de-saccaded eye velocity separately for upward and downward directions. To calculate a directional VOR gain, the cumulative change in eye position in each direction was then compared by the change in head position.

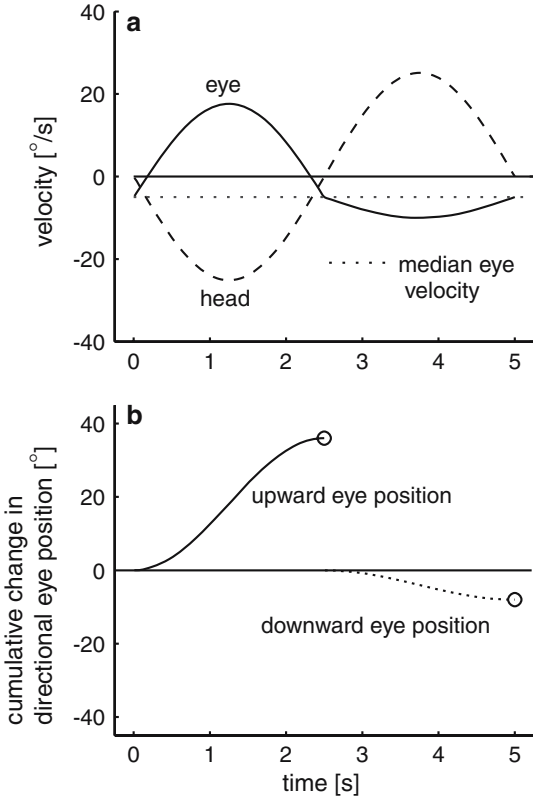

Fig. 2 Computation of directional VOR gain. One cycle of hypothetical vertical head oscillation (frequency: 0.2 Hz; amplitude: 20°; peak velocity: 25.1 deg/s) with asymmetric compensatory vertical eye movements (higher gain for downward than for upward head movements). **a** Traces of eye (*solid line*) and head (*dashed line*) velocity. Median eye velocity (*dotted line*) is below the zero baseline. **b** Cumulative changes of eye position computed from positive (*solid line*) or negative (*dotted line*) velocity values after subtracting the median velocity. The final positive and negative cumulative eye positions (*circles*) were divided by the corresponding cumulative head positions (not shown) to obtain upward and downward gains of the vestibulo-ocular reflex

Results

Figure 3 depicts cycles of median vertical eye velocity (see Methods) in a typical subject (S.M.) during testing of the VVOR in complete darkness before (black traces) and after (gray traces) symmetric (left column), selective pitch-up (middle column), and selective pitch-down (right column) VVOR cancellation. The median eye velocity before (horizontal black line) and after (horizontal gray line) the three paradigms is indicated as well. Before adaptation, average gains (pooled data from all three paradigms) for pitch-down (0.89, range: 0.88–0.90) and pitch-up (0.74, range: 0.70–0.82) VVOR were considerably asymmetric. After each of the three paradigms, the absolute gain reduction was computed separately for pitch-up and pitch-down directions. Symmetric VVOR cancellation induced a greater gain reduction in the pitch-down (absolute gain value reduced by 0.37 down to 0.52) than in the pitch-up direction (absolute gain value reduced by 0.29 down to 0.45). After selective cancellation of the pitch-up VOR, the pitch-up gain was decreased to 0.43 and the pitch-down gain to 0.59. Accordingly, selective pitch-down VOR cancellation led to a larger gain decrease for pitch-down (by 0.36 down to 0.53) than for pitch-up gain (by 0.17 down to 0.57).

Figure 4 summarizes pitch-down ('down') and pitch-up ('up') VOR gains and their differences in all eight subjects before and after adaptation. Before adaptation, average pitch-down (0.79 ± 0.19 STD) and pitch-up ($0.75 \pm$ STD) gains were not significantly different (paired t test: $P > 0.05$; upper left panel). Symmetric visual VVOR cancellation reduced the pitch-down gain (by 0.29 down to 0.50) more than the pitch-up gain (by 0.23 down to 0.52). Gains after symmetric adaptation, however, were not significantly different (paired t test: $P > 0.05$, lower left panel). Selective visual cancellation of the pitch-up VOR led to significantly smaller gains for pitch-up VOR (0.50 ± 0.16 STD) than for pitch-down VOR (0.61 ± 0.2 STD; paired t test: $P < 0.05$; upper right panel). Similarly, selective visual cancellation of the pitch-down VOR reduced the pitch-down gain (0.54 ± 0.16 STD) more than the pitch-up gain (0.59 ± 0.12 STD; paired t test: $P > 0.05$; lower right panel). Median eye velocities (representing "offset") and the moment during the oscillation cycle, when maximal

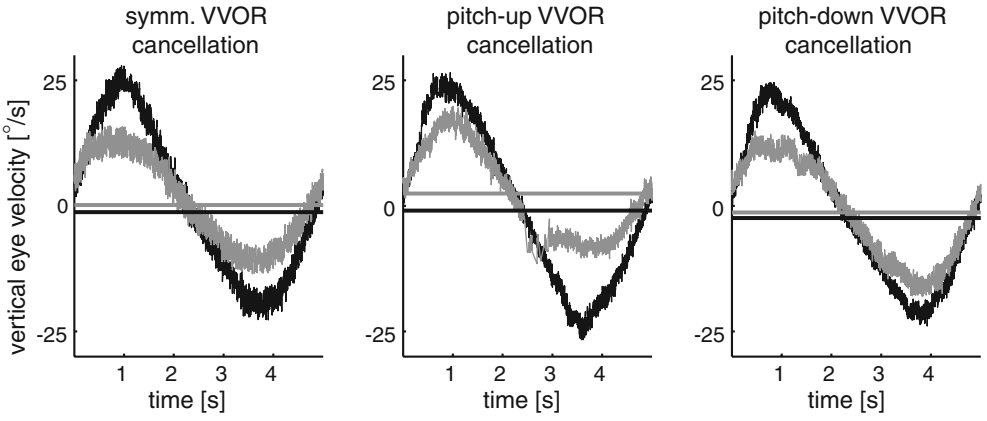

Fig. 3 Median vertical eye velocity traces (deg/s, *positive values* indicate upward directed eye velocity) of one typical subject (*S.M.*) during VVOR assessment in complete darkness before (*black traces*) and after (*gray traces*) symmetric visual VVOR cancellation (first column), selective visual cancellation of the pitch-up VOR (second column) and selective cancellation of the pitch-down VOR (third column). The *horizontal lines* indicate the median eye velocity before (*black line*) and after (*gray line*) symmetric and asymmetric VVOR cancellation paradigms. The traces were obtained by overlaying the vertical angular-velocity vectors of at least 12 oscillation cycles (0.2 Hz, ±20°) about the earth-vertical interaural axis and computing the median value for each millisecond (see Methods)

vertical eye position occurred (representing "phase") were not significantly affected by any of the adaptation paradigms (paired *t* tests: $P > 0.05$, not shown).

In a next step we asked whether the relative gain reduction induced by symmetric and asymmetric short-term adaptation was significantly different for pitch-up and pitch-down VOR. For both directions ('up', 'down'), Fig. 5 depicts the percentages of gain reduction (gain before = 100%) induced by symmetric (left column), selective pitch-up (middle column), and selective pitch-down (right column) visual VOR cancellation. The difference between the relative gain reductions ('diff', i.e. percent 'down' − percent 'up') and their average ('mean diff') are indicated as well.

Symmetric short-term adaptation induced a significantly larger VVOR gain reduction in the pitch-down (41%) than in the pitch-up (33%) direction (paired *t* test: $P < 0.01$). Gain reductions after asymmetric pitch-up (pitch-up: 32%; pitch-down 21%; paired *t* test: $P < 0.05$) and asymmetric pitch-down VOR adaptation (pitch-up:

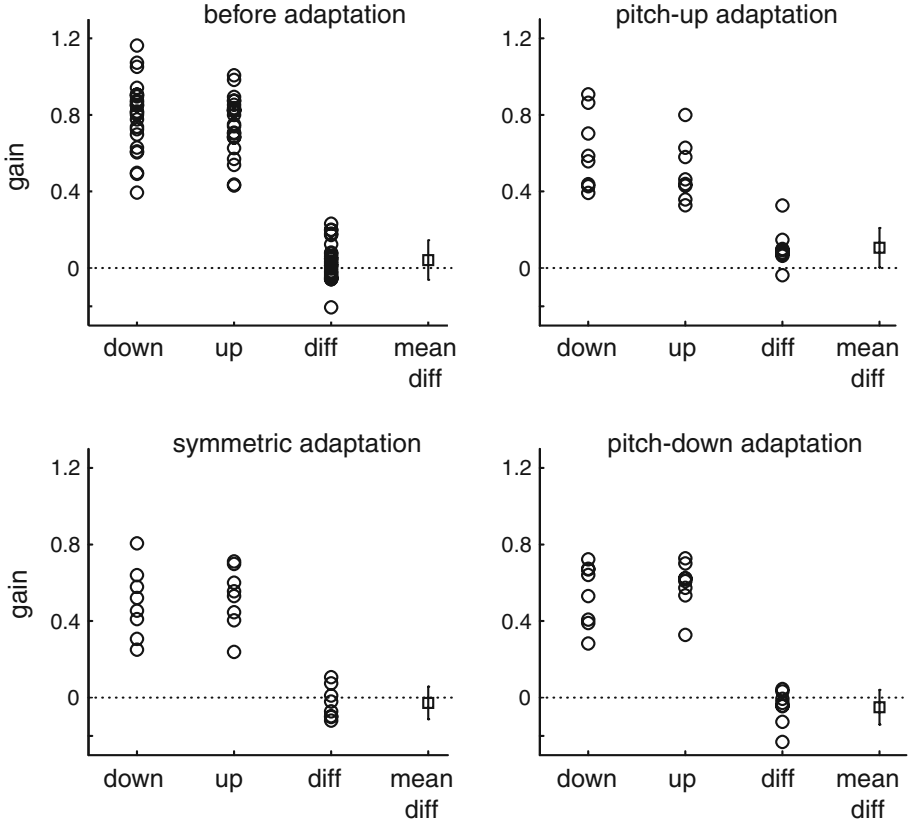

Fig. 4 Vertical vestibulo-ocular reflex VVOR gains in absolute values (*open circles*) assessed during oscillation (0.2 Hz, ±20°, about the earth-vertical interaural axis) in complete darkness in all eight subjects before (*upper left panel*) and after symmetric (*lower left panel*), selective pitch-up (*upper right panel*) and selective pitch-down (*lower right panel*) visual VVOR cancellation. Gain values for the downward ('down') and upward ('up') VOR, their differences ('diff', gain for downward VOR minus gain for upward VOR) and the average (±1 SD) difference ('mean diff') are depicted as well

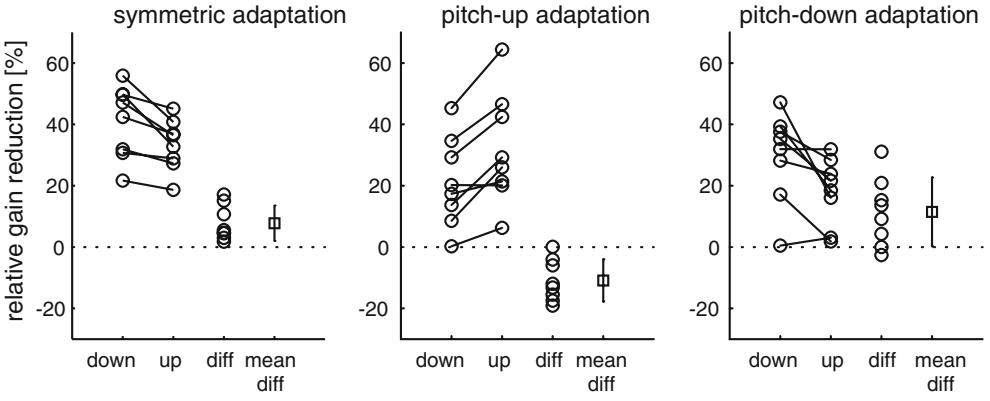

Fig. 5 Relative VVOR gain reductions after symmetric (*left panel*), selective pitch-up (*middle panel*) and selective pitch-down (*right panel*) visual VOR cancellation. Percentages of gain reductions in individual subjects (*open circles* connected by *solid line*) for the downward VOR ('down') and upward VOR ('up'), their differences ('diff', *open circles*, percentage of downward VOR gain reduction minus percentage of upward VOR gain reduction), and their average (±1 SD) difference ('mean diff') are depicted

18%, pitch-down 30%; paired t test: $P < 0.05$) were significantly larger in direction of the visual VVOR cancellation than in the untrained direction. The relative gain reduction in the trained direction was similar after asymmetric adaptation in the pitch-up (32%) and pitch-down (30%) direction (paired t test: $P > 0.05$). Likewise, the gain reduction in the untrained direction was not significantly different after pitch-up (21%) and pitch-down (18%) adaptation (paired t test: $P > 0.05$).

Discussion

Tracking of a moving target with the eyes and the head leads to visual cancellation of the VOR, mainly through activation of the smooth pursuit system (Lanman et al. 1978; Huebner et al. 1992), although other mechanisms, e.g. short-latency suppression of the VOR, may be involved as well (Kim and Sharpe 2001; Lisberger 1990). When visual VOR cancellation is sustained, the gain of the VOR decreases within minutes as a result of short-term adaptation processes. Our study is the first report of asymmetric adaptation of the human VVOR. Specifically, we examined the capacity for direction-selective VVOR adaptation by visual VOR cancellation using a smooth pursuit stimulus. We demonstrated that the human vertical vestibulo-ocular reflex can be adapted asymmetrically, and that upward and downward VOR pathways are equally adaptable. Symmetric visual VVOR cancellation, however, led to a significantly stronger gain reduction in the pitch-down than in the pitch-up direction, although no statistically significant difference between the gains for the pitch-up and pitch-down VOR was observed before adaptation.

Asymmetric adaptation of the VVOR and possible learning sites

The fact that induced gain reductions, although asymmetric, were not restricted to the direction of the visual cancellation stimulus, indicates an interdependence of mechanisms controlling the pitch-up and pitch-down VOR gains in humans. In monkeys, Hirata and coworkers (Hirata et al. 2002) studied whether upward and downward VOR gains can be modified simultaneously in opposite directions. Animals were exposed to visual–vestibular mismatch paradigms using optokinetic full-field stimulation that increased the VVOR gain in one direction and decreased the VVOR gain in the other direction, and the results indicated that the VVOR gain mechanisms are only partly interdependent between up and down. Our study comes to the same conclusion, but, in addition, demonstrates that visual VVOR cancellation by fixing upon a smooth pursuit stimulus is sufficient to asymmetrically adapt VVOR gains, at least in humans. In monkeys, it has already been shown that the tracking of a foveal pursuit stimulus is effective in adapting the horizontal VOR (Miles and Lisberger 1981a), but asymmetric VOR adaptation by pursuit stimuli has not been attempted so far.

It is well known from lesion studies that impairment of the flocculus (FL) abolishes the ability to modify VOR responses (Zee et al. 1981). The exact mechanisms by which the FL is involved in VOR learning is debated (Ito 1972, 1982; Miles and Lisberger 1981b; Watanabe 1984, 1985; Lisberger et al. 1994a, b; Hirata and Highstein 2001, 2002). According to the so-called multiple sites hypothesis (Miles and Lisberger 1981b; Lisberger et al. 1994a, b; Hirata and Highstein 2001, 2002), other sites for VVOR learning include floccular target neurons (FTNs) in the vestibular nucleus complex and in group Y, which receive inhibitory input from floccular Purkinje cells (PCs; Chubb and Fuchs 1982; Partsalis et al. 1995a, b; Blazquez et al. 2000). Probably, these FTNs are provided by the FL with an error signal containing information on direction and magnitude of gain changes (Hirata and Highstein 2002). Most PCs in the cerebellar flocculus are sensitive to gaze-velocity signals (Miles et al. 1980; Stone and Lisberger 1990), and respond preferentially to smooth pursuit eye movements during VOR cancellation, but modulate only a little during normal VOR in the dark. With regard to our adaptation paradigms, visual cancellation of the VOR was most probably achieved by activation of the smooth pursuit system. Therefore, an important role of gaze-velocity-sensitive

floccular PCs in the adaptation process is highly plausible.

Mechanism of asymmetric VVOR adaptation by symmetric VVOR cancellation

Symmetric short-term adaptation of the VVOR induced by visual cancellation reduced the pitch-down gain significantly more than the pitch-up VOR gain, i.e. symmetric visual VVOR cancellation was more effective in the downward direction. How can this predominance of the downward visual VOR cancellation be explained? Possibly, this finding could reflect asymmetrical directional sensitivities of involved floccular PCs. Most gaze-velocity PCs roughly exhibit either horizontal or vertical on-directions (Miles et al. 1980; Stone and Lisberger 1990; Fukushima et al. 1999). Interestingly, the large majority of vertical gaze-velocity PCs have downward on-directions, i.e. they increase their firing rate in response to downward eye movements during smooth pursuit or VVOR cancellation, while the resting rate decreases during upward eye movements.

With regard to our VVOR adaptation paradigms, it can be assumed that the majority of vertical gaze-velocity-sensitive floccular PCs increased their firing rate during downward VOR cancellation and decreased their firing rate in response to upward VOR cancellation. Since symmetric VVOR cancellation induced a significantly greater gain reduction for the pitch-down than for the pitch-up VOR, one could hypothesize that the increase of the PCs firing rate during downward VOR cancellation was greater than the decrease during upward VOR cancellation. This notion is supported by the finding that the change of simple spike activity in vertical floccular gaze-velocity PCs in monkeys during vertical smooth pursuit was larger in the on-direction (downward, increase of firing rate) than in the off-direction (upward, decrease of firing rate; Stone and Lisberger 1990). In other words, the sensitivity of these cells is smaller at lower spike frequencies. Although Stone and Lisberger did not test the visual VVOR suppression in their study, it seems reasonable to assume that vertical floccular gaze-velocity-sensitive PCs show a similar non-linearity of their discharge modulation in response to upward and downward VOR cancellation as for smooth pursuit. The combination of such non-linear discharge modulation and the asymmetric directional sensitivities could probably explain, why, in our experiments, the symmetric visual VVOR cancellation by the smooth pursuit system led to a greater gain reduction in the downward direction.

Conclusion

We have shown that the human VVOR system is capable of asymmetric adaptation, and that during symmetric visual VVOR cancellation pitch-down adaptation is more effective.

Our results provide evidence for interdependent mechanisms for control of pitch-up and pitch-down VOR gains. In the cerebellar flocculus, one of the main neural structures involved in the VVOR gain control, the combination of the strong asymmetry in on-directions of vertical floccular gaze-velocity PC cells and their direction-selective non-linear response pattern may account for the observed asymmetry in gain reduction after symmetric visual VVOR cancellation. To further explore this hypothesis, fMRI studies in humans could be useful.

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